DETAILED ACTION

This action is in response to the amendment, filed 2/16/2010, in which claim 34 was amended, and claim 65 was newly added. It is noted that the amendment to the claims filed 12/1/2009 was not entered. Thus, claim 65 should have the status identifier "new." The nature of the non-compliance did not preclude an exanimation on the merits. Claims 24-37, 39, 40, 46-65 are pending and under consideration.

Any rejection of record in the previous office actions not addressed herein is withdrawn. New grounds of rejection are presented herein that were not necessitated by applicant's amendment of the claims since the office action mailed 9/16/2009. Therefore, this action is not final.

Claim Objections

Claim 65 is objected to because of the following informalities: the claim language is confusing due to the wording of the claim, the abbreviations, and the missing commas. If the abbreviations were to be spelled out, the claim would recite "chimeric protein of ecdysone receptors glucocorticoid receptor activation domain and DNA binding domain and herpesvirus transactivation domain *Heliothis virescens* ecdysone receptor ligand binding domain." It is clear from the teachings of the prior art (Martinez et al. The Plant Journal, Vol. 19, No. 1, pages 97-106, 1999) that the claim is directed to a DNA fragment that comprises a nucleic acid sequence encoding a chimeric ecdysone receptor protein comprising a glucocorticoid receptor (GR) activation domain, a GR DNA binding domain (DBD), a herpesvirus transactivation domain, and

a *Heliothis virescens* ecdysone receptor (HEcR) ligand binding domain (LBD). Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 24-29, 31, 32, 37, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Rasochova et al (US Patent Application Publication No. 2003/0074677 A1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

Regarding claim 24, Rasochova et al teach a DNA molecule comprising cDNA of an RNA virus vector that has been constructed by inserting an exogenous RNA component and a ribozyme sequence at the 3' region (e.g., paragraph [0049]). Rasochova et al teach the DNA molecule where the exogenous RNA component has a coding function in which the RNA acts as a messenger RNA, encoding a sequence which, when translated by the host cell, results in the synthesis of a peptide or protein (e.g., paragraph [0047]).

Regarding claims 25-29, Rasochova et al teach the DNA molecule where the virus vector originates in a virus that is a single strand (+) RNA virus, such as barley stripe mosaic virus or tobacco mosaic virus (e.g., paragraphs [0042], [0135], [0139] and [0141]).

Regarding claim 31, Rasochova et al teach the DNA molecule where the exogenous RNA component is inserted in place of the coat protein coding sequence (e.g., paragraphs [0057] and [0137]).

Regarding claim 32, Rasochova et al teach the DNA molecule, where the promoter that directs the expression of the exogenous RNA and ribozyme is an inducible promoter (e.g., paragraphs [0049]-[0050]).

Regarding claim 37, Rasochova et al teach a vector that comprises the DNA molecule and is capable of being incorporated into a cellular genome (e.g., paragraphs [0008]-[0010] and [0044]).

Regarding claim 39, a kit is a collection of items. Rasochova et al teach a DNA fragment and vector comprising cDNA of an RNA virus vector that has been constructed by inserting an exogenous RNA component and a ribozyme sequence at the 3' region (e.g., paragraph [0049]). Rasochova et al teach the DNA molecule where the exogenous RNA component has a coding function in which the RNA acts as a messenger RNA, encoding a sequence which, when translated by the host cell, results in the synthesis of a peptide or protein (e.g., paragraph [0047]). Thus, Rasochova et al teach the claimed kit.

Regarding claim 40, Rasochova et al teach a transformant obtained by transfection of a plant cell with a vector comprising a DNA fragment comprising cDNA of an RNA virus vector that has been constructed by inserting an exogenous RNA component and a ribozyme sequence at the 3' region (e.g., paragraphs [0009], [0010], [0049], [0054] and [0058]). Rasochova et al teach the DNA molecule where the exogenous RNA component has a coding function in which

the RNA acts as a messenger RNA, encoding a sequence which, when translated by the host cell, results in the synthesis of a peptide or protein (e.g., paragraph [0047]).

Claims 24-26, 30, 31, 37, 39 and 40 are rejected under 35 U.S.C. 102(b) as being anticipated by Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

Regarding claim 24, Mori et al teach a DNA fragment comprising a cDNA of a Brome mosaic virus that has been constructed by inserting a coding sequence of a human gamma interferon (IFN) protein into the RNA virus, and ligating a ribozyme sequence to the 3' end of the virus vector cDNA (e.g., page 85, paragraph bridging columns; Figure 1).

Regarding claims 25 and 26, Mori et al teach the DNA fragment wherein the virus vector originates in a virus that is a Brome mosaic virus, which is a single strand (+) RNA plant virus (e.g., page 80, right column, 2nd full paragraph).

Regarding claim 30, Mori et al teach the DNA fragment where the ribozyme sequence is a ribozyme sequence of satellite tobacco ringspot virus (e.g., page 85, paragraph bridging columns).

Regarding claim 31, Mori et al teach the DNA fragment where the IFN sequence was inserted in place of the coat protein gene (e.g., page 80, right column, 2nd full paragraph).

Regarding claim 37, Mori et al teach a vector comprising the DNA fragment, where the vector is capable of being incorporated into a cellular genome (e.g., paragraph bridging pages 80-81).

Regarding claim 39, a kit is a collection of items. Mori et al teach a DNA fragment and a vector comprising a cDNA of a Brome mosaic virus that has been constructed by inserting a coding sequence of a human gamma interferon (IFN) protein into the RNA virus, and a ribozyme sequence ligated to the 3' end of the virus vector cDNA (e.g., page 85, paragraph bridging columns; Figure 1). Thus, Mori et al teach the kit of claim 39.

Regarding claim 40, Mori et al teach a transformant of *N. benthamiana*, which is obtained with a vector including a cDNA of a Brome mosaic virus that has been constructed by inserting a coding sequence of a human gamma interferon (IFN) protein into the RNA virus, and a ribozyme sequence ligated to the 3' end of the virus vector cDNA (e.g., page 85, paragraph bridging columns; Figure 1).

Response to Arguments - 35 USC § 102

With respect to the rejection of claims 24-29, 31, 32, 37, 39 and 40 under 35 U.S.C. 102(b) as being anticipated by Rasochova et al, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that Rasochova does not teach or suggest "cDNA of a virus vector that has been constructed by inserting a coding gene of an arbitrary protein into an RNA virus" as recited in independent claim 24. The response that Rasochova teaches a DNA-launching platform encoding a modified viral RNA molecule including an RNA viral component attached to an exogenous RNA component. Further, the response asserts that Rasochova does not teach or suggest "a ribozyme sequence ligated to the 3' end of the virus vector cDNA." The response

asserts that Rasochova teaches a nucleotide sequence encoding a self-cleavable ribozyme situated proximate to the 3' end of the RNA molecule.

This argument is not found persuasive. Rasochova et al define "DNA-launching platform" to mean a DNA molecule, circular or linear, which has a coding region comprising a segment encoding a modified viral RNA segment, and further, which is capable of being delivered into a cell and subsequently transcribed" (paragraph [0049]). Rasochova et al teach the DNA molecule encoding a viral RNA molecule into which an exogenous RNA is introduced (e.g., paragraphs [0007] and [0049]). Rasochova et al teach that "exogenous RNA" is a term used to describe a segment or component of RNA to be inserted into the virus RNA to be modified (e.g., paragraph [0047]). Rasochova et al specifically teach that the RNA may act as a messenger RNA encoding a sequence which, when translated by the host cell, results in synthesis of a peptide or protein having useful or desired properties (e.g., paragraph [0047]). This is the "coding gene of an arbitrary protein" of the instant claims. Further, Rasochova et al teach that the DNA-launching platform further comprises a nucleotide sequence encoding a self-cleavable ribozyme situated proximate to the 3' end of the modified viral RNA (e.g., paragraph [0049]). This is the ribozyme sequence ligated to the 3' end of the virus vector cDNA of the present claims. Although Rasochova et al do not use the same wording as presented in the rejected claims, the structures are the same. Thus, Rasochova et al teach each element of the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 24-26, 30, 31, 37, 39 and 40 under 35 U.S.C. 102(b) as being anticipated by Mori et al, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that Mori does not teach or suggest "cDNA of a virus vector that has been constructed by inserting a coding gene of an arbitrary protein into an RNA virus" as recited in independent claim 24. The response asserts that Mori teaches inserting a RNA1-cDNA fragment into a binary transformation vector.

These arguments are not found persuasive. Mori et al teach a Brome mosaic virus cDNA into which a coding sequence for the interferon (IFN) gene has been inserted (e.g., page 80, right column, 1st and 2nd paragraphs; page 85, paragraph bridging columns). Although Mori et al do not use the same wording as presented in the rejected claims, the structures are the same. Thus, Mori et al teach each element of the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 32-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of Zuo et al (US Patent No. 6,452,068 B1, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

The teachings of Mori et al are described above and applied as before.

Mori et al do not teach the DNA fragment where the cDNA of the virus vector that has incorporated the IFN coding sequence and the ribozyme sequence ligated to the 3' end of the virus vector are transcribed under control of an inducible promoter that is located upstream of the virus vector cDNA and ribozyme sequence, where the inducible promoter is (i) 6XUASgal4 or (ii) O_{LexA}-46, and the DNA fragment further comprises a transcription factor for controlling transcription induced by the inducible promoter, where the transcription factor is (i) GVG or (ii) XVE.

Zuo et al teach a single vector comprising a promoter operably linked to a transcription factor and a promoter regulated by the transcription factor operably linked to a protein coding gene (e.g., column 9, line 27 to column 11, line 2). Zuo et al teach the vector where the transcription factor is a chimeric transcription factor in which the regulatory region of the rat

glucocorticoid receptor (GR) is added to the DNA-binding domain of the yeast transcription factor GAL4 and the transactivating domain of the herpes viral protein VP16, where the chimeric transcription factor is called GVG (e.g., column 9, lines 50-67). When the vector comprises the GVG transcription factor, the inducible promoter contains six copies of the GAL4 upstream activating sequence (UAS) (6xUASGal4, e.g., column 9, lines 50-67; Figure 1). Zuo et al teach another construct referred to as XVE, which is similar to the GVG system but contains the DNA binding domain of the bacterial repressor LexA and the regulatory region of the human estrogen receptor (e.g., column 10, lines 43-53). Zuo et al specifically teach that the XVE construct can be used in place of the GVG construct as long as the proper inducer is used for the construct being used (e.g., column 10, lines 48-51). When the vector comprises the XVE transcription factor, the inducible promoter contains eight copies of LexA binding sites fused to the 35S minimal promoter at -46 (O_{LexA}-46; e.g., paragraph bridging columns 20-21; Figure 13).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the vector of Mori et al to include the GVG coding sequence and the IFN coding sequence on the same vector as taught by Zuo et al because Zuo et al teach it is within the ordinary skill in the art to use a single vector for expression of a transcription factor for regulating an inducible promoter and for expression of a protein operably linked to the inducible promoter when the GVG transcription factor and 6XUASgal4 promoter is contained in the vector. With regard to claim 36, it would have been obvious to further modify the single vector comprising the GVG coding sequence and 6XUASgal4 sequence to replace the GVG coding sequence with the XVE coding sequence and to replace the 6XUASgal4 promoter with the

O_{LexA}-46 promoter, because Zuo et al specifically teach that the XVE system can be used in place of the GVG system as long as the appropriate inducer is used.

One would have been motivated to make such a modification in order to receive the expected benefit of reducing the transformation and crossing steps to bring the GVG coding sequence and IFN coding sequence into the same plant cell as taught by Mori et al (e.g., page 82, *Production of transgenic plants containing cDNA of RNA1 or cDNAs of both RNA2 and FCP2IFN*; pages 82-83, *Induced replication of FCP2IFN and subgenomic mRNA amplification in GVG1 x 2FR plants*) to a single step based on the production of a single vector containing all necessary elements of the inducible system, as taught by Zuo et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 46-48, 50, 51 and 55-64 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of David et al (Plant Physiology, Vol. 125, pages 1548-1553, April 2001, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

Mori et al teach a process for producing a transformant for protein production, comprising (i) transforming *N. benthamiana* host cells with a GVG transcription factor-expressing DNA fragment in which the GVG coding sequence is operably linked to the CaMV 35S promoter; where transforming is done by an Agrobacterium method (ii) screening the

transformants obtained in step (i) for an individual F0 plant expressing GVG; and (iii) crossing the F0 GVG-expressing plants with 2FR plants containing cDNA of a virus vector that has been constructed by inserting a coding gene of human gamma interferon (IFN) into an RNA virus, where the IFN coding sequence is ligated to the 6XUASGal4 inducible promoter, which is induced by the GVG transcription factor (e.g., page 82, *Production of transgenic plants containing cDNA of RNA1 or cDNAs of both RNA2 and FCP2IFN*; pages 82-83, *Induced replication of FCP2IFN and subgenomic mRNA amplification in GVG1 x 2FR plants*; page 85, *Transformation of Nicotiana benthamiana*; Figure 1). Specifically, the virus vector used in the method of Mori et al contains a cDNA of a Brome mosaic virus that has been constructed by inserting a coding sequence of a human gamma interferon (IFN) protein into the RNA virus, and ligating a ribozyme sequence to the 3' end of the virus vector cDNA (e.g., page 85, paragraph bridging columns; Figure 1). The ribozyme sequence is a ribozyme sequence of satellite tobacco ringspot virus (e.g., page 85, paragraph bridging columns). In the virus vector, the IFN sequence was inserted in place of the coat protein gene (e.g., page 80, right column, 2nd full paragraph). Further, Mori et al teach a transformant produced by the abovementioned process, where the transformant produces IFN protein in the presence of dexamethasone (e.g., Figure 4). Mori et al teach that the GVG transcription factor has a property of being activated by the hormone dexamethasone, a synthetic steroid hormone (e.g., page 82, *Analysis of the accumulation of RNA1 in response to DEX treatment*). Mori et al teach the method where the virus vector originates in a virus that is a Brome mosaic virus, which is a single strand (+) RNA plant virus (e.g., page 80, right column, 2nd full paragraph). With regard to claim 64, a kit is a collection of

items, and Mori et al teach at least one item for use in the process of producing the abovementioned transformant (e.g., page 85, Experimental procedures).

Mori et al do not teach the method where the GVG transformants are further transformed with the cDNA of a virus vector that encodes IFN using an Agrobacterium method. Further, Mori et al do not teach the method where the cells are tobacco BY-2 cells.

David et al teach that the tobacco (*Nicotiana tabacum*) BY2 cell line is well characterized, highly homogenous, and shows an exceptionally high growth rate (e.g., page 1548, left column, 1st paragraph). Further, David et al teach that BY2 cells can be easily transformed without the need for protoplast preparation and stable transgenic calli, and suspension-cultured cells are easily obtained (e.g., page 1548, left column, 1st paragraph). David et al teach a method that brings together the advantages of the BY2 cell line with the advantages of the tetracycline derepressible system (e.g., page 1548, right column, full paragraph). David et al teach a method for producing a transformant for protein production, comprising (i) transforming BY2 cells with pBinTet1 vector, containing tetR under the control of the cauliflower mosaic virus (CaMV)-35S promoter; (ii) selecting clonal and stable transformants, named BY2-tetR, on kanamycin medium; (iii) and transforming the BY2-tetR cells with a pTX-Gus-int, a vector containing β-glucuronidase (Gus) under the control of the "Triple-Op" promoter coupled with CaMV 35S (e.g., paragraph bridging pages 1548-1549; page 1549, left column). David et al teach that Gus activity was induced in the BY2-tetR cells comprising pTX-Gus-int by the addition of AhTc (e.g., Figure 1). David et al teach that a high steady-state expression of tetR ensures an efficient repression of the "Triple-Op" promoter (e.g., paragraph

bridging pages 1549-1550). David et al teach Agrobacterium-mediated transformation of the BY2 cells (e.g., page 1552, Cell Transformation).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Mori et al to include a first Agrobacterium-mediated transformation step of BY2 cells with the GVG expression vector, and a second Agrobacterium-mediated transformation step of BY2 cells with the IFN expression vector, as taught by David et al because David et al teach it is within the ordinary skill in the art to use BY2 cells for regulated expression of a protein product and Mori et al teach regulated expression of the IFN protein product.

One would have been motivated to make such a modification in order to receive the expected benefit of selecting for BY2 GVG transformants with desirable levels of GVG expression prior to transformation with the IFN expression vector, because David et al teach that desirable levels of tetR could be identified prior to the second transformation step. It would have been within the ordinary skill of the art to transform the BY2 cells based upon the teachings of David et al, and it would have been within the skill of the art to screen for desirable levels of GVG by Northern blotting as taught by Mori et al. Furthermore, one would have been motivated to perform a second transformation step in BY2 cells rather than produce plants and cross the plants as taught by Mori et al in order to save time, because David et al teach that BY2 cells have an exceptionally high growth rate and are easy to transform. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of David et al (Plant Physiology, Vol. 125, pages 1548-1553, April 2001; see the entire reference) as applied to claims 46-48, 50, 51 and 55-64 above, and further in view of Zuo et al (US Patent No. 6,452,068 B1; see the entire reference). This rejection was made in the Office action mailed 9/16/2009 and is reiterated below.

The combined teachings of Mori et al and David et al are described above and applied as before.

Mori et al and David et al do not teach the method where the transcription factor is LexA-VP16-hER, the inducible promoter is O_{LexA}-46, and the inducer is estrogen.

Zuo et al teach the vector where the transcription factor is a chimeric transcription factor in which the regulatory region lf the rat GR is added to the DNA-binding domain of the yeast transcription factor GAL4 and the transactivating domain of the herpes viral protein VP16, where the chimeric transcription factor is called GVG (e.g., column 9, lines 50-67). When the vector comprises the GVG transcription factor, the inducible promoter contains six copies of the GAL4 upstream activating sequence (UAS) (6xUASGal4, e.g., column 9, lines 50-67; Figure 1). Zuo et al teach another construct referred to as XVE, which is similar to the GVG system but contains the DNA binding domain of the bacterial repressor LexA and the regulatory region of the human estrogen receptor (e.g., column 10, lines 43-53). Zuo et al specifically teach that the XVE construct can be used in place of the GVG construct as long as the proper inducer is used for the construct being used (e.g., column 10, lines 48-51). When the vector comprises the XVE

transcription factor, the inducible promoter contains eight copies of LexA binding sites fused to the 35S minimal promoter at -46 (O_{LexA}-46), and the inducer is estrogen (e.g., Example 12; Figure 13).

Mori et al and David et al both teach the use of regulatable transcription factors capable of being modulated for regulated expression of a protein. Mori et al specifically teaches the use of the GVG system, and Zuo et al specifically teaches that it was within the skill of the art to substitute the XVE system for the GVG system in order to achieve the predictable result of providing inducible expression of a protein. The XVE system comprises the claimed LexA-VP16-hER transcription factor, which is activated by estrogen, and the O_{LexA}-46 promoter.

Claims 52-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of David et al (Plant Physiology, Vol. 125, pages 1548-1553, April 2001; see the entire reference) as applied to claims 46-48, 50, 51 and 55-64 above, and further in view of Rasochova et al (US Patent Application Publication No. 2003/0074677 A1; see the entire reference).

The combined teachings of Mori et al and David et al are described above and applied as before.

Mori et al and David et al do not teach the method where the virus vector comprises tobacco mosaic virus.

Rasochova et al teach a vector comprising cDNA of an RNA virus vector that has been constructed by inserting an exogenous RNA component and a ribozyme sequence at the 3' region

(e.g., paragraph [0049]). Rasochova et al teach the vector where the exogenous RNA component has a coding function in which the RNA acts as a messenger RNA, encoding a sequence which, when translated by the host cell, results in the synthesis of a peptide or protein (e.g., paragraph [0047]). Rasochova et al teach the vector where the virus vector originates in a virus that is a single strand (+) RNA virus, such as tobacco mosaic virus (e.g., paragraphs [0042], [0135], [0139] and [0141]). Rasochova et al teach the DNA molecule where the exogenous RNA component is inserted in place of the coat protein coding sequence (e.g., paragraphs [0057] and [0137]). Rasochova et al teach the use of the vector to make transgenic plants expressing the protein (e.g., paragraphs [0138]-[0141]). Further, Rasochova et al teach it is within the skill of the art to use an inducible promoter for the expression of the exogenous RNA component (e.g., paragraphs [0049]-[0050]).

Because Mori et al and Rasochova et al both teach vectors for the expression of a protein in plant cells, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tobacco mosaic virus vector of Rasochova et al for the Brome mosaic virus vector of Mori et al, where expression of the protein is under the control of the 6xUASgal4 promoter, in order to achieve the predictable result of providing a vector for the inducible expression of a protein in a plant cell.

Claims 32-34 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mori et al (The Plant Journal, Vol. 27, No. 1, pages 79-86, 2001, cited on the IDS filed 3/31/2006; see the entire reference) in view of Martinez et al (The Plant Journal, Vol. 19, No. 1,

pages 97-106, 1999; see the entire reference). This is a new rejection, necessitated by the addition of new claim 65 in the reply filed 2/16/2010.

The teachings of Mori et al are described above and applied as before.

Mori et al do not teach the DNA fragment where the cDNA of the virus vector that has incorporated the IFN coding sequence and the ribozyme sequence ligated to the 3' end of the virus vector are transcribed under control of an inducible promoter that is located upstream of the virus vector cDNA and ribozyme sequence, wherein the inducible promoter is GRE, the transcription factor that controls transcription induced by the inducible promoter is a chimeric protein of ecdysone receptors GR Act and DBD and herpesvirus transactivation domain HecR LBD, and the inducer is ecdysone.

Martinez et al teach a vector comprising an inducible GRE promoter upstream of a sequence to be transcribed and translated, and upstream of an expression cassette for the expression of a ligand-regulated transcription factor (e.g., Figure 1(b)). Martinez et al teach a vector encoding a transcription factor where the transcription factor is a chimeric protein comprising sequences of ecdysone receptors (EcR), glucocorticoid receptors (GR), and herpesvirus sequence (e.g., pages 97-98, Introduction; Figure 1). Martinez et al teach that HecR or HEcR refers to *Heliothis virescens* ecdysone receptor (e.g., paragraph bridging pages 97-98; page 98, paragraph bridging columns; page 99, right column, full paragraph; Figure 1(b)). Specifically, Martinez et al teach a vector encoding GR Act, herpesvirus VP16 transactivation domain, GR DBD, and HEcR LBD (e.g., Figure 1(b)). This vector encodes a chimeric protein of ecdysone receptors that comprises GR Act and DBD, herpesvirus transactivation domain, and HecR LBD. Martinez et al teach that the chimeric protein is inducible by the steroid hormone

ecdysone or the ecdysone analog muristeroneA (e.g., paragraph bridging pages 97-98; page 100, left column, 1st full paragraph; page 103, left column, last full paragraph). Addition of muristeroneA to a plant transformed with the vector ES-60, which encodes the chimeric transcription factor, results in activation of expression from GRE also present in the vector, leading to detection of GUS protein (e.g., page 100, left column, 1st full paragraph; Figure 1(b)). Martinez et al teach that the inducible system is flexible, in that a strong activator (i.e., VP16) has been successfully used to enhance performance and is useful in both research and commercial applications (e.g., page 103, left column, last full paragraph).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the DNA fragment of More et al, which comprises the IFN coding sequence in place of the RNA virus coat protein, to include a GRE promoter upstream of the RNA virus and 3' ribozyme sequence, as well as the expression cassette encoding the ecdysone-responsive transcription factor taught by Martinez et al because Mori et al teach it is within the ordinary skill in the art to regulate the expression of the IFN gene indirectly using the inducible GVG system, and Martinez et al teach that the GRE and ecdysone-responsive transcription factor can be used for regulated expression.

One would have been motivated to make such a modification in order to receive the expected benefit of using a flexible system that acts as a strong activator of transcription as taught by Martinez et al. Further, one would have been motivated to directly regulate the expression of the viral RNA and IFN gene with fewer vectors. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the

contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 32-36 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of Zuo et al, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that Zuo does not remedy the deficiencies of Mori with respect to independent claim 24.

This argument is not found persuasive for the reasons set forth above with regard to the anticipation of claim 24 by the teachings of Mori et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 46-48, 50, 51 and 55-64 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that Mori does not teach or suggest "a second transforming step of transfecting the transformant, obtained in the screening step, with a protein-expressing DNA fragment in which cDNA of a virus vector that has been constructed by inserting a coding gene of an arbitrary protein into an RNA virus is ligated to an inducible promoter which is induced by the transcription factor" as recited in independent claim 46. The response asserts that Mori teaches inserting a RNA1-cDNA fragment into a binary transformation vector instead of

constructing cDNA of a virus vector by inserting a coding gene of an arbitrary protein into an RNA virus.

These arguments are not found persuasive. While Mori et al do teach inserting a RNA1-cDNA fragment into a binary transformation vector, the reference is prior art for all that it teaches. Mori et al further teach a Brome mosaic virus cDNA into which a coding sequence for the interferon (IFN) gene has been inserted (e.g., page 80, right column, 1st and 2nd paragraphs; page 85, paragraph bridging columns). Mori et al teach transforming the vector into cells to make a plant comprising the vector. However, it was noted in the rejection of record that Mori et al do not teach the method where the GVG transformants are further transformed with the cDNA of a virus vector that encodes IFN using an Agrobacterium method. This deficiency is met by the combined teachings of Mori et al and David et al. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claim 49 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al, and further in view of Zuo et al, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that the Examiner has failed to show how David and Zuo remedies the deficiencies of Mori with respect to independent claim 24. Thus, the response asserts that

claim 49 is patentable over Mori and David and Zuo for the reasons set forth above with respect to independent claim 24.

These arguments are not found persuasive for the reasons set forth above with regard to the anticipation of claim 24 by Mori et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 52-54 under 35 U.S.C. 103(a) as being unpatentable over Mori et al in view of David et al, and further in view of Rasochova et al, Applicant's arguments filed 2/16/2010 have been fully considered but they are not persuasive.

The response asserts that the Examiner has failed to show how David and Rasochova remedy the deficiencies of Mori with respect to independent claim 46. Thus, the response asserts that claims 52-24 are patentable over Mori and David and Rasochova for the reasons set forth above with respect to independent claim 46.

These arguments are not found persuasive for the reasons set forth above with regard to the obviousness of claim 46 over the combined teachings of Mori et al and David et al.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Examiner
Art Unit 1636